AMENDMENTS TO THE DRAWINGS

The attached drawing sheet includes changes to Figure 5. Please note, the actual figure remains the same, however, that portion of the title referring to Antibody As Tracer, should read: (with PTH 1-[[8]]9 Antibody as Tracer).

Please replace Figure 5 with the presently submitted amended Figure 5.

Attachment: Replacement sheet

REMARKS

Paragraph beginning at page 1, line 20 of the present specification is amended to reflect the status of the two parent applications.

Figure 5 is amended to reflect the inventor's belief that PTH 1-9 antibody was used as a tracer antibody in the test results depicted in Figure 5. (*See* Ex. A., Cantor Declaration) The use of a PTH 1-9 antibody in a PTH assay is supported throughout the present application as originally filed. For example, Figure 2 of the present application illustrates a tracer antibody that binds to an epitope within PTH (1-9) sequence.

Claims 47-107 were previously submitted for examination. Claims 47-68 and 98-107 were withdrawn from consideration. Claims 1-46 were canceled by the Preliminary Amendment submitted on January 16, 2004 and claims 72-77, 85, 87-91 and 94 have been canceled by the present Amendment. Claims 69, 78-84, 86, 92, 95 and 96 are amended. Therefore claims 69-71, 78-84, 86, 92, 93 and 95-97 are under active consideration.

Support for the amended claims 69, 78, 86 and 92 for reciting "said isolated antibody binds to said three-dimensional epitope within a whole PTH with a higher affinity than its binding to said three-dimensional epitope within a PTH fragment" can be found in an inherent binding property of an exemplary anti-PTH antibody used in the whole PTH assay as described in the present application, *e.g.*, at page 8, lines 24 and 25 of the present specification, and in Figure 11. This inherent binding property is described in Rebuttal Expert Report of Richard A. Lerner, M.D. (Lerner Report) (Ex. B) at paragraph 5, pages 5-8 and Exhibits 2-7 of the Lerner Report.

Support for the amended claims 69, 78 and 92 for reciting "said isolated antibody does not specifically bind to a non-(1-84) or non-(1-86) PTH fragment" can be found throughout the present application, and *inter alia*, at page 8, lines 24 and 25 of the present specification, and in Figure 11, which shows that the an exemplary anti-PTH antibody used in the whole PTH assay specifically binds to the whole PTH molecule but does not specifically bind to an exemplary non-(1-84) PTH fragment, PTH (7-84).

Support for the amended claim 86 can be found throughout the present application, and *inter alia*, at page 11, lines 7-13 and page 12, line 7 through page 13, line 4 of the present specification.

According, the present amendments to the specification, drawings and claims do not add any new matter. Entry of the amendments is respectfully requested.

With respect to all amendments and canceled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Election/Restrictions

The Examiner made the following restriction requirement:

I. Claims 47-68, drawn to a method of producing antibodies to human PTH, classified in class 436, subclass 536.

II. Claims 69-97, drawn to PTH antibodies, classified in class 530, subclass 389.2.

111, Claims 98-107, drawn to a method for detecting bioactive PTH, classified in class 435, subclass 7.1.

Applicants hereby confirm the previous provisional election of Group II, claims 69-97 made in a telephonic interview between the Examiner and the undersigned on October 11, 2006.

Claim Rejections under 35 U.S.C. § 102

Rejection over Fischer

Claims 69-80, 83-85 and 88-96 are rejected under 35 U.S.C. 102(b) as being allegedly anticipated by Fischer *et al.*, *J. Clin. Investigation* 1974 Vol. 54, page 1382 (Fischer). According to the Examiner:

- With respect to claims 69, 80, 88, 89, 91, 92 and 95, Fischer *et al.* teach isolated antibodies that recognizes and binds to the bioactive, three dimensional epitope, *i.e.* 1-12 or 1-34, of parathyroid hormone (PTH) (*See* Abstract).

- With respect to claims 70 and 75, the antibodies used by Fischer *et al.* recognize the amino terminus of human PTH. Surpa.

- With respect to claims 72-77, 85 and 94, the antibody recognizing 1-12 is within the recited range from 1-13 of SEQ ID No. 1 of the human PTH starting from amino-terminal Ser in position 1 to Lys in the position 13. surpa.

- With respect to claims 79, the antibodies inherently can reduce the adenylate cyclase activity of PTH because the position of the epitope of PTH. Surpa.

- With respect to claim 86, Fischer *et al.* teach immunization of animals with the PTH peptides and recovering antibodies from the animals and isolating the PTH antibodies (*See* Method).

- With respect to claims 84, 93 and 96, Fischer *et al.* teach using isotopes to label antibodies for detection purpose (*See* Methods).

Applicants respectfully traverse this rejection and submit that Fischer does not disclose each and every element of the presently pending claims 69-71, 78-84, 86, 92, 93 and 95-97. For

example, the presently pending claims 69-71, 78-84, 86, 92, 93 and 95-97 are directed to an isolated antibody, or an isolated antibody, that specifically binds to a bioactive, three-dimensional epitope of a parathyroid hormone (PTH). Fischer does not disclose any isolated anti-PTH antibody at all. Fischer discloses immunizing goats with a urea-trichloroacetic acid extract of human parathyroid tumors [(hPTH-(TCA)], synthetic hPTH (1-12) peptide, synthetic hPTH (1-34) peptide and purified bovine PTH (1-84) [bPTH (1-84)]. (*See* Fischer, the "*Peptides*" Section at pages 1383-1384, and the "*Immunization and quantification of antibodies*" Section at page 1385.) After the sera were collected, the "sera were heat inactivated (56°C, 30 min) and stored in small portions at - 20°C until use." (*Id.*) The sera or antisera were tested without any isolation or purification. (*Id.*) Claim 86 also requires a step of isolating the polyclonal antibody by binding the polyclonal antibody to at least four amino acids in the common sequence of human and rat PTH (1-8) sequence. Fischer does not disclose any antibody isolation step, let alone the recited specific isolation step of claim 86.

In addition, claims 69-71, 78-84, 86, 92, 93 and 95-97 further require that the isolated antibody binds to the three-dimensional epitope within a whole PTH with a higher affinity than its binding to said three-dimensional epitope within a PTH fragment. Fischer does not disclose this limitation for several reasons. First, epitopes can be various types. Both linear and conformational, *i.e.*, three-dimensional epitopes, are known in the art:

> Several categories of epitope have been defined for protein antigens, based on the proximity of the relevant amino acids in the primary structure of the protein (Fig. 14.3). The simplest case is the *linear* epitope, where all of the amino acids constituting the epitope are derived from a contiguous stretch of the polypeptide chain. However, many - perhaps most - epitopes on globular proteins involve amino acids from two or more stretches of polypeptide that are distant from one another in the primary structure. Such an epitope is referred to as *conformational* or *discontinuous*.

(Ex. C, Rich et al., *Clinical Immunology Principles and Practice*, Second Ed., Mosby (2001) at 14.4.) Because the conformational or the three-dimensional epitopes are formed from two or more stretches of polypeptide that are distant from one another in the primary structure, this means that the conformational or the three-dimensional epitopes are better formed when the entire protein is at

its natural conformation. This also means that perturbing the natural conformation of the entire protein, *e.g.*, making a fragment from the entire protein containing the conformational or the three-dimensional epitopes, may very well perturb the conformational or the three-dimensional epitopes situated in a non-natural environment. It follows that if an antibody binds to a three-dimensional epitope, the antibody should bind to the entire protein, which contains the three-dimensional epitope in its natural environment, better than binding to the same three-dimensional epitope in a fragment of the protein.

An exemplary antibody described in the present application, *i.e.*, the anti-PTH antibody generated by immunizing goat with a whole PTH molecule and then isolated by affinity purification with an N-terminal PTH fragment, binds to a three-dimensional epitope within the whole PTH molecule. In the previous Nichols v. Scantibodies litigation, the binding property of the labeled antibody of Scantibodies' whole PTH tests was tested for its binding affinity to the whole PTH molecule and a number of short N-terminal PTH peptides, including the peptide that was used in the affinity purification of the antibody. (*See* Ex. B, Rebuttal Expert Report of Richard A. Lerner, M.D. (Lerner Report) at paragraph 5, pages 5-8 and Exhibits 1-7 of the Lerner Report.) Based on the test results recorded in Exhibits 2-7 of the Lerner Report, Dr. Lerner concluded:

> In summary, the direct ELISA analysis of the PTH(1-9) antibody and the PTH(1-12) antibody shows that neither binds to the peptides of PTH 1-5, 1-6, 1-7, 1-8 and 1-10. While each of the two antibodies exhibits some binding with the 1-9 peptide of PTH, <u>they have a much higher binding affinity for the entire PTH molecule (1-84) than with the 1-9 peptide</u>.

(The Lerner Report at page 7; emphasis added.) The testing data described in the Lerner Report indicate that the labeled antibody of Scantibodies' whole PTH tests binds to a three-dimensional epitope within the whole PTH molecule because the antibody binds to the epitope within the whole PTH molecule better than binding to the epitope in a short PTH peptide.

In contrast, as expected, the antisera generated by immunization with synthetic hPTH (1-12) peptide and synthetic hPTH (1-34) peptide in Fischer bind to its respective epitope in the hPTH (1-12) peptide and the hPTH (1-34) peptide better than binding to its respective epitope in the whole

PTH molecule. For example, the ability of various PTH peptides and proteins to inhibit the binding between a radioactively labeled hPTH (1-12) peptide and the antisera generated using the synthetic hPTH (1-12) peptide was tested and the results were shown and described in Figure 3, and at pages 1387-1388 of Fischer. The ID_{50}'s, *i.e.*, the concentration needed to achieve 50% inhibition, for the hPTH (1-34) and hPTH (1-84) is from 2.9 times to 18.3 times of the D_{50}'s of the hPTH (1-12) peptide. (*See* Fischer, Figure 3, and the description at pages 1387-1388.) The similar inhibition tests were conducted on the antisera generated using the hPTH (1-34) peptide and the similar results were observed. (*See* Fischer, Figure 4, and the description at page 1388, the "full length human extracted peptide had an ID_{50} approximately 30 times higher than the ID_{50} of the homologous inhibitor [*i.e.*, the hPTH (1-34) peptide]."") These testing data in Fischer indicate that the antisera generated by immunization with synthetic hPTH (1-12) peptide and synthetic hPTH (1-34) peptide do not meet the limitation that the isolated antibody binds to the three-dimensional epitope within a whole PTH with a higher affinity than its binding to said three-dimensional epitope within a PTH fragment.

Further, the hPTH (1-84), *i.e.*, the hPTH-(TCA), and bPTH (1-84) used in Fischer to generate antisera were crude extract and/or not sufficiently purified. "The estimated purity [of the hPTH-(TCA)] was 10%" and the bPTH (1-84) "was assumed to have a purity of 79%." (*See* Fischer, the "*Peptides*" Section at pages 1383-1384.) It is well recognized in the art that parathyroid tissue or cells produce both whole PTH and other non-(1-84) parathyroid hormone (PTH) fragments or amino-terminal (N) truncated fragments. For example, using HPLC separation and radioactive protein sequencing, D'Amour et al. isolated the non-(1-84) PTH fragments from parathyroid tissue or cells and determined that the interfering non-(1-84) PTH fragment is a group of large N-terminal PTH fragments of PTH (4-84) to PTH (15-84), PTH (7-84) being the dominant one. (Ex. D, D'Amour et al., *Kidney International*, 68:998-1007 (2005) at page 998, Conclusion; and page 1006, Table 3.) Because the crude or not sufficiently purified parathyroid tissue or cell extract was used in Fischer, it is expected that the antisera generated using the extract would contain antibodies that would bind to both the whole PTH molecule and the non-(1-84) PTH fragments. Accordingly, the antisera generated by immunization with the hPTH-(TCA) and the bPTH (1-84) would not meet the

limitation that the isolated antibody does not specifically binds to a non-(1-84) or non-(1-86) PTH fragment.

In view of the foregoing, applicants respectfully request reconsideration and withdrawal of the anticipation rejection of claims 69-80, 83-85 and 88-96 over Fischer.

Rejection over Magerlein (I)

Claims 69-80, 83-85, 88-96 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Magerlein *et al. Pharmaceutical Sciences,* 1994, Vol. 2, page 117-194 Abstract [Magerlein (I)]. According to the Examiner:

- With respect to claims 69, 75, 76, 80, 81, 88, 89, 91, 92 and 95, Magerlein *et al.* (I) teach an isolated antibody that recognizes and binds to the bioactive, three dimensional epitope, *i.e.* 1-5 or 1-34 , of parathyroid hormone (PTH) (*See* Abstract).

- With respect to claims 70 and 75, the antibodies used by Magerlein *et al.* (I) recognize the amino terminus of human PTH. Surpa.

- With respect to claims 72-74, 76, 77, 85 and 94, the antibody recognizing 1-5 is within the recited range from 1-13 of SEQ ID No. 1 of the human PTH starting from amino-terminal Ser in position l to Lys in the position 13. surpa.

- With respect to claims 79, the antibodies inherently can reduce the adenylate cyclase activity of PTH because the position of the epitope of PTH. Surpa.

- With respect to claims 84, 93 and 96, Magerlein *et al.* (I) teach two-sites immunoassay (*e.g.* labeling antibodies) for detection purpose. Supra.

Applicants respectfully traverse this rejection and submit that Magerlein (I) does not disclose each and every element of the presently pending claims 69-71, 78-84, 86, 92, 93 and 95-97. For example, the presently pending claims 69-71, 80-84, 86 and 92, 93 and 95-97 require that the isolated antibody binds to the three-dimensional epitope within a whole PTH with a higher affinity than its binding to said three-dimensional epitope within a PTH fragment. In Magerlein (I), the antibody is generated by immunization with a synthetic hPTH 1-10 peptide. Magerlein (I) does not disclose immunization with a whole PTH molecule. As discussed above in connection with the anticipation rejection over Fischer, an antibody generated using a short peptide will bind better to the short peptide than its binding to an entire protein containing the peptide, as shown in Fischer. Magerlein (I) does not disclose any data to show that its anti-PTH antibody binds to the three-dimensional epitope within a whole PTH with a higher affinity than its binding to said three-dimensional epitope within a PTH fragment. Absent such showing, there is no explicit anticipation of the presently pending claims, and any anticipation rejection must be based on an inherency theory.

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. MPEP § 2112.IV *citing In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

Given the fact that the antibody is generated by immunization with a synthetic hPTH 1-10 peptide Magerlein (I), and the data in Fischer that the antibody generated using a short peptide binds to the short peptide better than binding to an entire protein containing the peptide, it is

unlikely that the antibody generated using a hPTH 1-10 peptide in Magerlein (I) would bind better to the whole PTH molecule than binding to the hPTH 1-10 peptide. Therefore, there would be no inherent anticipation of the presently pending claims over Magerlein (I).

In view of the foregoing, applicants respectfully request reconsideration and withdrawal of the anticipation rejection of claims 69-80, 83-85 and 88-96 over Magerlein (I).

Rejection over Magerlein (II)

Claims 69-81, 83-85 and 88-96 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Magerlein *et al.*, *Arzneim-Forsch/Drug Res* 1998 Vol. 48, page 783-787 [Magerlein (II)]. According to the Examiner:

- With respect to claims 69, 75, 80, 81, 88, 89, 91, 92 and 95, Magerlein *et al.* (II) teach an isolated antibody that recognizes and binds to the bioactive, three dimensional epitope, *i.e.* 1-10 , of parathyroid hormone (PTH.) (*See* Abstract).

- With respect to claims 70, the antibodies used by Magerlein *et al.* (II) recognize the amino terminus of human PTH. Surpa.

- With respect to claims 72-74, 76, 77, 85 and 94, the antibody recognizing 1-10 is within the recited range from 1-13 of SEQ ID No. 1 of the human PTH starting from amino-terminal Ser in position 1 to Lys in the position 13. surpa.

- With respect to claims 79, the antibodies inherently can reduce the adenylate cyclase activity of PTH because the position of the epitope of PTH. Surpa.

- With respect to claims 84, 93 and 96, Magerlein *et al.* (I) teach ELISA immunoassay (*e.g.* labeling antibodies) for detection purpose (*See* Methods).

Applicants respectfully traverse this rejection and submit that Magerlein (II) does not disclose each and every element of the presently pending claims 69-71, 78-84, 86, 92, 93 and 95-97 for the same reason that Magerlein (I) does not disclose each and every element of the presently pending claims.

In view of the foregoing, applicants respectfully request reconsideration and withdrawal of the anticipation rejection of claims 69-80, 83-85 and 88-96 over Magerlein (II).

Rejection over Colford

Claims 69-81, 83-85 and 88-96 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Colford *et al.*, Endocrine Society 79th Meeting, June 11-14 1997 Minneapolis, Minnesota; (Colford). According to the Examiner:

- With respect to claims 69, 75, 80, 81, 88, 89, 91, 92 and 95, Colford *et al.* teach an isolated antibody that recognizes and binds to the bioactive, three dimensional epitope, *i.e.* 1-7 or 1-14 of parathyroid hormone (PTH) (*See* Abstract).

- With respect to claims 70, the antibodies used by Colford *et al.* recognize the amino terminus of human PTH. Surpa.

- With respect to claims 72-74, 76, 77, 85 and 94, the antibody recognizing 1-10 is within the recited range from 1-13 of SEQ ID No. 1 of the human PTH starting from amino-terminal Ser in position l to Lys in the position 13. surpa.

- With respect to claims 79, the antibodies inherently can reduce the adenylate cyclase activity of PTH because the position of the epitope of PTH. Surpa.

- With respect to claims 84, 93, 96, Colford *et al.* teach ELISA immunoassay (*e.g.* labeling antibodies) for detection purpose (*See* Abstract).

Applicants respectfully traverse this rejection and submit that Colford does not disclose each and every element of the presently pending claims 69-71, 78-84, 86, 92, 93 and 95-97. For example, the presently pending claims 69-71, 78-84, 86, 92, 93 and 95-97 require that the isolated antibody binds to the three-dimensional epitope within a whole PTH with a higher affinity than its binding to said three-dimensional epitope within a PTH fragment. Colford refers to a PTH (1-7) antibody and the use of the PTH (1-7) antibody in testing various PTH forms after HPLC separation. Contrary to the Examiner's assertion, Colford does not disclose any PTH (1-14) antibody. Colford states that "PTH (1-14) appears to be necessary for receptor activation upon receptor binding." (*See* Colford Abstract.) This is a discussion about the potential function of the PTH (1-14) region on the PTH molecule itself. It is not a disclosure about any anti-PTH (1-14) antibody. In any case, Colford does not disclose any data to show that its PTH (1-7) antibody binds to a three-dimensional epitope within a whole PTH, or that the PTH (1-7) antibody binds to the three-dimensional epitope within a whole PTH with a higher affinity than its binding to said three-dimensional epitope within a PTH fragment.

In addition, claim 86 requires the steps of immunizing an animal with human whole PTH as a primary immunization, immunizing the animal with human whole PTH subsequent to the primary immunization, recovering a polyclonal antibody from the animal, and isolating the polyclonal antibody by binding said polyclonal antibody to at least four amino acids in the common sequence of human and rat PTH (1-8) sequence. Colford does not provide any information as to how its PTH (1-7) antibody was generated, characterized, and/or purified, if it was purified at all.

Further, the presently pending claims 69-71, 80-84, 86 and 92, 93 and 95-97 require that the isolated antibody does not specifically bind to a non-(1-84) or non-(1-86) PTH fragment. As discussed above, Colford does not provide any information as to how its PTH (1-7) antibody was generated, characterized, and/or purified, if it was purified at all. In any case, Colford's own data demonstrate that Colford "PTH (1-7) antibody" does bind to a non-(1-84) or non-(1-86) PTH fragment. If the Colford "PTH (1-7) antibody" does not specifically bind to a non-(1-84) or non-(1-86) PTH fragment, the Colford "PTH (1-7) antibody" would be able to distinguish whole PTH from an interfering non-(1-84) PTH fragment, *e.g.*, PTH (7−84). As shown in detail below, Colford's

own experiments demonstrate that its "PTH (1-7) antibody" is incapable of distinguishing whole PTH from an interfering non-(1-84) PTH fragment.

According to Colford *et al.*, Endocrine Society 79th Annual Meeting 1997, pages IMU-3282 to IMU-3297 (Colford) (Ex. E), three peaks containing PTH, PTHα peak, PTHβ peak and PTHγ peak, were detected by the Nichols Allegro™ intact PTH test in various HPLC fractions. (Colford at page IMU-3288.) An immunoassay using the PTH (1-7) antibody referred to in Colford detected the forms of PTH contained in the PTHα peak and, to a lesser degree, the forms of PTH contained in the PTHβ peak. (*Id.*) According to Colford, PTHα peak contains the unfragmented whole PTH (1-84 PTH) and PTHβ and PTHγ contain unspecified N-terminal PTH fragments (*Id.* at page IMU-3289.) The immunoassay using the PTH (1-7) antibody referred to in Colford had meaningful cross-reactivity for PTHβ (*i.e.*, the PTH (1-7) antibody measured certain amount of the PTH forms contained in the PTHβ peak compared to the percent measured by the Nichols Allegro IRMA intact PTH assay).

Both the 1997 Colford Abstract (Ex. F, Colford et al., The Endocrine Society, Program & Abstracts, 79th Annual Meeting, June 11-14, 1997, Minneapolis Minnesota, and entitled "Isolation and Characterization of Large Molecular Weight Fragments of PTH") and Colford refer to a "PTH (1-7) antibody." (Ex. F, 1997 Colford Abstract, and Ex. E, Colford at pages IMU-3283, IMU-3284 and IMU-3288.) The poster from the 1996 Annual Meeting of the Endocrine Society, San Francisco, CA, U.S.A., Todd Jensen, Jon Spring, and John Colford, entitled "Comparing Specificity for Intact Human Parathyroid Hormone between INCSTAR PTH SP and NICHOLS INTACT PTH ASSAYS" (Jensen 1996 Poster) (Ex. G) refers to "EXP (1-7)." (Ex. G, Jensen 1996 Poster at pages 4, 5 and 9.) According to Colford, The "EXP (1-7)" in the Jensen 1996 Poster refers to an immunoassay for PTH in which the "PTH (1-7) antibody" referred to in 1997 Colford Abstract and Colford was used (*i.e.*, the antibody used in the EXP (1-7) assay and the PTH (1-7) assay are one and the same). (Ex. H, A copy of Declaration of John Colford submitted in the reexamination of the parent patent U.S. Patent No. 6,689,566 B1 (Reexam Control Nos. 90/007,685 and 90/007,732).)

As shown in Jensen 1996 Poster, in many instances, the immunoassay using the "PTH (1-7) antibody" gave higher or comparable PTH test results from the PTH test results obtained using Nichols Allegro™ IRMA Intact PTH test. (Ex. G, Jensen 1996 Poster at page 9.) It is known in the art that Nichols Allegro™ IRMA Intact PTH test cannot distinguish a whole PTH from an interfering non-(1-84) PTH fragment, *e.g.*, PTH 7-84 fragment. As demonstrated in Gao et al., *J. Bone Miner. Res.*, 16(4):605-14 (2001):

> Assay specificity to synthetic PTH (7-84) was studied by comparing this whole PTH IRMA [developed by Scantibodies Laboratories, Inc.] with Nichols intact PTH IRMA. Nearly 100% cross-reaction to this fragment was observed with Nichols intact PTH assay, but no cross-reaction was detected with this newly developed whole PTH IRMA even at a PTH (7-84) concentration of 10,000 pg/ml (Fig. 2).

(*See* Ex. I, Gao et al., *J. Bone Miner. Res.*, 16(4):605-14 (2001), Figure 2, at page 608.) Accordingly, the higher or comparable PTH test results from the immunoassay using the "PTH (1-7) antibody" indicate that this PTH assay cannot distinguish a whole PTH from a N-terminal PTH fragment as well. The inability of the immunoassay using Colford "PTH (1-7) antibody" to distinguish whole PTH from an interfering non-(1-84) PTH fragment demonstrates that Colford "PTH (1-7) antibody" does not meet the limitation that the isolated antibody does not specifically binds to a non-(1-84) or non-(1-86) PTH fragment recited in the presently pending claims.

In view of the foregoing, applicants respectfully request reconsideration and withdrawal of the anticipation rejection of claims 69-80, 83-85 and 88-96 over Colford.

Claim Rejections under 35 U.S.C. § 103

Magerlein (I-II) or Colford in view of Gotschlich

Claims 82, 86 and 87 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over either Magerlein (I-II) or Colford *et al.* in view of Gotschlich *et al.*, US patent No. 5,545,553 (Gotschlich). Gotschlich is alleged to teach that using humanized antibody provides

for the advantage of inducing much less immune response than xenogenic antibodies, in particular an allergic response (Col. 20, line 14-20). The Examiner alleged that it would have been obvious to one ordinary skill in the art at the time the invention was made to have provided Magerlein (I-II) or Colford with the humanized antibody as taught by Gotschlich in order to reduce allergic response in the immunoassay of patients. With respect to claim 86 and 87, Gotschlich is alleged to teach using the keyhole limpet hemocyanin as a linker carrier to produce antibody (Col. 19, line 47-52). It is allegedly a well-known and widely practiced procedure to immunize animals and recovering antibodies from the immunized animals.

Applicants respectfully traverse this rejection and submit that Magerlein (I), Magerlein (II) or Colford in view of Gotschlich does not render claims 82 and 86 obvious. As discussed above in connection with the anticipation rejections, Magerlein (I), Magerlein (II) or Colford fails to teach all the elements of the presently pending claim 69, from which claim 82 depends, and claim 86. For example, Magerlein (I), Magerlein (II) or Colford fails to teach one or more of the following limitations:

- The isolated antibody binds to the three-dimensional epitope within a whole PTH with a higher affinity than its binding to said three-dimensional epitope within a PTH fragment.

- The steps of immunizing an animal with human whole PTH as a primary immunization, immunizing the animal with human whole PTH subsequent to the primary immunization, recovering a polyclonal antibody from the animal, and isolating the polyclonal antibody by binding said polyclonal antibody to at least four amino acids in the common sequence of human and rat PTH (1-8) sequence.

- The isolated antibody does not specifically bind to a non-(1-84) or non-(1-86) PTH fragment.

Gotschlich does not cure the deficiencies of Magerlein (I), Magerlein (II) or Colford because Gotschlich does not teach any anti-PTH antibody at all. Therefore, even assuming that there is a motivation to combine, the combination of Magerlein (I), Magerlein (II) or Colford with Gotschlich, does not teach all the limitations of claims 82 and 86.

In addition, the rejection of claim 87 is rendered moot by the cancellation of claim 87.

In view of the foregoing, applicants respectfully request reconsideration and withdrawal of the anticipation rejection of claims 82, 86 and 87 over Magerlein (I), Magerlein (II) or Colford in view of Gotschlich.

Magerlein (I-II) or Colford in view of Chang

Claim 97 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over either Magerlein (I-II) or Colford *et al.* in view of Chang *et al.*, U.S. patent No. 4,824,777 (Chang). Chang is alleged to teach using a variety of means to label antibody, including enzymatic, fluorogenic, radiometric and chemiluminescent labels. One of the compound allegedly taught by Chang is acridinium ester (Col. 3, line 1-10). The Examiner alleged that it would have been obvious to one ordinary skill in the art at the time the invention was made to have provided Magerlein (I-II) or Colford with the alternative label compound such as acridinium ester as taught by Chang because using different alternative label means to label antibody is well-known in the art, and it merely involves routine practice.

Applicants respectfully traverse this rejection and submit that Magerlein (I), Magerlein (II) or Colford in view of Chang does not render claim 97 obvious. As discussed above in connection with the anticipation rejections, Magerlein (I), Magerlein (II) or Colford fails to teach all the elements of the presently pending claim 92, from which claim 97 depends. For example, Magerlein (I), Magerlein (II) or Colford fails to teach one or more of the following limitations:

- The isolated antibody binds to the three-dimensional epitope within a whole PTH with a higher affinity than its binding to said three-dimensional epitope within a PTH fragment.

- The isolated antibody does not specifically bind to a non-(1-84) or non-(1-86) PTH fragment.

Chang does not cure the deficiencies of Magerlein (I), Magerlein (II) or Colford because Chang does not teach any anti-PTH antibody at all. Therefore, even assuming that there is a motivation to combine, the combination of Magerlein (I), Magerlein (II) or Colford with Chang does not teach all the limitations of claim 97.

In view of the foregoing, applicants respectfully request reconsideration and withdrawal of the anticipation rejection of claim 97 over Magerlein (I), Magerlein (II) or Colford in view of Chang.

Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue or to make a finding as to whether there is any interfering subject matter between the pending claims of the present application and that of US 2006-0286107 A1 (U.S. Application No. 11/437,428), which claims priority from US 2003/0082179 A1 (U.S. Application No. 09/898,398). If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **532212000624**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: March 23, 2007

Respectfully submitted,

By_____

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